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# Toxicological Problems Associated with Chlorine Dioxide

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16. ABSTRACT
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# Toxicological Problems Associated With Chlorine Dioxide

*Lyman W. Condie*

**The toxicological hazards associated with disinfecting drinking water with either chlorine dioxide or chlorine are reviewed and compared. Adverse health effects shown in animal experiments as well as human poisoning incidents are reported. Toxicological effects, which are associated with the disinfectants themselves and the products formed when the disinfectants react with organic material present in water, are considered.**

The disinfection of public water supplies has been used to prevent the transmission of waterborne diseases throughout the world. Although chlorine ($Cl_2$) has been used as the primary disinfectant in the United States, its safety was first questioned in 1974 when chlorination of drinking water was found to result in the formation of trihalomethanes (THMs).[1,2] Additional concerns were raised in 1976 when the National Cancer Institute reported that chloroform, a by-product of chlorination, produced an increased incidence of tumors in experiments with two animal species.[3]

The initial response to these observations was to examine alternative disinfectants that would not produce THMs. Chlorine dioxide ($ClO_2$) was selected as one alternative disinfectant, but it became apparent that little was known about the possible health hazards of $ClO_2$ or its reaction by-products.

The Toxicology and Microbiology Division of the Health Effects Research Laboratory (TMD-HERL) of the US Environmental Protection Agency (USEPA) has been conducting and sponsoring toxicological research to evaluate the possible adverse health effects of the various disinfectants and their by-products. Research results that have become available since publication of an earlier review of toxicological problems associated with alternative disinfectants are emphasized.[4] Some studies concerning the effects of these two disinfectants on humans are presented.

## Health effects of chlorine dioxide, chlorite, and chlorate

Numerous studies have been conducted with $ClO_2$ and its inorganic by-products—chlorite ($ClO_2^-$) and chlorate ($ClO_3^-$). Because $ClO_2$ disproportionates to form $ClO_2^-$ and $ClO_3^-$ in alkaline solutions and because $ClO_2$ decomposes to yield $ClO_3^-$ in acidic solutions with exposure to sunlight, the toxicity of $ClO_2^-$ and $ClO_3^-$ must be considered in evaluating the safety of $ClO_2$ as a disinfectant. Because $ClO_2$ and $ClO_3^-$ can be rapidly converted to $ClO_2^-$ in humans, some aspects of their toxicity are probably similar. Table 1 summarizes some short- and long-term exposure studies evaluating the toxicity of $ClO_2$, $ClO_2^-$, and $ClO_3^-$, which have been reported in the literature.

Toxicological effects from exposure to $ClO_2$, $ClO_2^-$, and $ClO_3^-$ were first associated with the hemopoietic system. Work at TMD-HERL indicated that $ClO_2^-$ produced hemolytic anemia at lower exposure levels than those required to produce significant increases in methemoglobin.[5] The hemolytic anemia was associated with oxidative damage to the red blood cell membrane. Additional studies extended these findings to $ClO_2$ and $ClO_3^-$.[6,7] Chlorite remained the most potent of the three chemical species for causing signs of hemolytic oxidative stress in animals. These effects were seen in varying degrees of sensitivity in several species.[8]

The ability of disinfectants to induce hematological effects in monkeys was evaluated by Bercz et al.[9] Disinfectant in the monkeys' drinking water was increased in a stepwise fashion; thus each animal served as its own control. Hematological effects were observed with $ClO_2^-$ and $ClO_3^-$ but not with $ClO_2$. Monkeys exposed to $ClO_2$ displayed dose-related decreases in serum thyroxine levels. The hypothyroid effect was unique to $ClO_2$ because its breakdown products, $ClO_2^-$ and $ClO_3^-$, did not produce a depression of serum thyroxine levels, even at higher exposure doses than the $ClO_2$ exposure levels.

Reproductive and developmental studies were also performed. In one study, female mice were exposed to $ClO_2^-$ in drinking water from the time of breeding until the time of weaning.[10] At weaning the growth rates and body weights of pups from dams exposed to $ClO_2^-$ were significantly lower than they were in the control group. In another study, dams were exposed to extreme levels of $ClO_2^-$, which resulted in an increase in stillbirths and fetal resorptions.[11] This effect may be due to anoxia induced by the hemolytic effects of $ClO_2^-$, rather than a direct effect on prenatal development. Although adverse effects on maternal reproductive ability in animals used for experiments have not been reported, one study reported a decreased drive range for sperm and an increased percentage of abnormal sperm in male rats exposed to drinking water containing 100 or 500 mg $ClO_2^-$/L.[12] A separate study did not detect sperm-head abnormalities in mice exposed to $ClO_2$, $ClO_2^-$, and $ClO_3^-$.[13]

A recent study[14] suggests that developing rats exposed to $ClO_2$ indirectly via the dam's drinking water (100 mg/L) from 14 days prior to breeding until the pups were 21 days old, or directly by oral gavage from 5 through 20 days old (14 mg/kg/d), resulted in significantly depressed serum thyroxine levels in 21-day-old pups. Because $ClO_2$ appears to exert an antithyroid effect in developing animals and because thyroid function is intimately involved with the control of neurobehavioral development, it was not surprising that developing rats exposed to $ClO_2$ exhibited delayed brain development and behavior.[15]

Recent experimental findings suggest that $ClO_2$, but not $ClO_2^-$, might increase cardiovascular disease risk by increasing plasma cholesterol levels and increasing the size of plaques in blood vessels of pigeons that received a diet high in lipid and marginal in calcium.[16] These observations are being verified.

The mutagenic potential of $ClO_2$, $ClO_2^-$, and $ClO_3^-$ was evaluated in the mouse micronucleus assay, the mouse bone marrow chromosomal aberration assay, and the mouse sperm-head abnormality assay.[13] Chemicals were administered by aqueous gavage for five consecutive days. No evidence of any mutagenic activity was detected with any of these chemicals.

Chlorite was first tested for its ability to act as a tumor promoter or as a complete carcinogen.[17] In the complete carcinogen test, 100 mg/kg $ClO_2^-$ was applied twice weekly to the shaved backs of Sencar mice for 51 weeks. For the testing of $ClO_2^-$ as a tumor promoter, a single initiating dose of 20 μmol of dimethylbenzanthracene (DMBA) was applied preceding the 51-week application of $ClO_2^-$. No tumors were detected in the complete carcinogenicity test. However, six of the twenty mice that received a prior dose of DMBA developed skin tumors. Those that received DMBA followed by acetone treatments for 51

**TABLE 1**

*Summary of oral exposure studies with chlorine dioxide ($ClO_2$), sodium chlorite ($NaClO_2$), and sodium chlorate ($NaClO_3$)*

| Study | Chemical Substances | Species | Exposure Time | Toxicological Endpoint | Gavage Dose or Drinking Water Concentration—mg/L NOAEL* | LOAEL† |
|---|---|---|---|---|---|---|
| Heffernan et al[5] | $NaClO_2$ | Rat | Acute | Methemoglobinemia | | 20 |
| | | | 70 days | Increased RBC‡ turnover | 10 | 100 |
| | | | | Decreased hematocrit and Hb§ | | 500 |
| | | Rat | Up to 90 days | Decreased GSH** in RBC | 10 | 50 |
| | | | | Decreased RBC and Hb | | 100 |
| Moore and Calabrese[6] | $ClO_2$ | Mouse | 30 days | Hematologic | 100 | |
| | $NaClO_2$ | Mouse | 30 days | Decreased Hb, increased RBC osmotic fragility | 10 | 100 |
| Couri and Abdel-Rahman[7] | $ClO_2$ | Rat | 12 months | Increased glutathione peroxidase | 10 | 100 |
| | | Mouse | 12 months | Increased catalase | 1 | 10 |
| | $NaClO_2$ | Rat | 12 months | Decreased GSH in RBC | 10 | 100 |
| | $NaClO_3$ | Rat | 12 months | Inconsistent hematologic changes | | |
| Bercz et al[9] | $ClO_2$ | Monkey | 42 days | Decreased serum $T_4$†† levels | 30 | 100 |
| | | | | | 100 | |
| | $NaClO_2$ | Monkey | 42 days | Decreased RBC | 50 | 100 |
| | $NaClO_3$ | Monkey | 42 days | Decreased RBC and Hb | | 25 |
| Moore and Calabrese[10] | $NaClO_2$ | Mouse | Mating through weaning | Decreased pup growth rate, lower body weight at weaning | | 100 |
| Couri et al[11] | $NaClO_2$ | Rat | Days 8–15 of gestation | Smaller litter size, more stillbirths and fetal resorptions | 5000 | 20 000 |
| Meier et al[13] | $ClO_2$ | Mouse | 5 days | Sperm-head abnormalities, mutagenicity | 16 mg/kg/d | |
| | $NaClO_2$ | Mouse | 5 days | Sperm-head abnormalities, mutagenicity | 40 mg/kg/d | |
| | $NaClO_3$ | Mouse | 5 days | Sperm-head abnormalities, mutagenicity | 40 mg/kg/d | |
| Orme et al[14] | $ClO_2$ | Rat | Two weeks before mating through weaning | Decreased serum $T_4$ levels, slowed development | 20 | 100 |
| | $ClO_2$ | Rat | Gavage days 5–20 | Decreased serum $T_4$ levels, slowed development | | 14 mg/kg/d |
| Revis et al[16] | $ClO_2$ | Pigeon | 90 days | Decreased plasma thyroid hormones, increased plasma cholesterol, increased plaque size | 2 | 15 |
| | $NaClO_2$ | Pigeon | 90 days | Decreased plasma thyroid hormones, increased plasma cholesterol, increased plaque size | 15 | |
| Lubbers et al[21] | $ClO_2$ | Human | 1 day | Hematologic, serum chemistry, urinalysis | 24 | |
| | | Human | 84 days | Hematologic, serum chemistry, urinalysis | 5 | |
| | $NaClO_2$ | Human | 1 day | Hematologic, serum chemistry, urinalysis | 2.4 | |
| | | Human | 84 days | Hematologic, serum chemistry, urinalysis | 5 | |
| | $NaClO_3$ | Human | 1 day | Hematologic, serum chemistry, urinalysis | 2.4 | |
| | | Human | 84 days | Hematologic, serum chemistry, urinalysis | 5 | |

*NOAEL—no-observed-adverse-effect level
†LOAEL—lowest-observed-adverse-effect level
‡RBC—red blood cell
§Hb—hemoglobin
**GSH—glutathione
††$T_4$—thyroxine

weeks developed no tumors. Five of the six animals developed squamous cell carcinomas. This result, however, was statistically nonsignificant.

Possible tumor-promoting effects of sodium chlorate ($NaClO_3$) and potassium chlorate ($KClO_3$) were tested in a two-stage, 25-week renal carcinogenesis bioassay of rats with $NaClO_3$ and $KClO_3$ at a 1-percent level in drinking water.[18] Under the conditions of the experiment, $NaClO_3$ and $KClO_3$ did not demonstrate a carcinogenic effect.

Because of the extensive use of $ClO_3^-$ as a weed killer, there are a number of reports of $ClO_3^-$ poisoning in humans. Effects after estimated ingested doses of up to 3400 mg/kg include cyanosis, methemoglobinemia, renal failure, congested kidneys, hypothermia, convulsions, and coma. The lowest lethal doses were about 220 mg/kg in adults[19] and 250 mg/kg in infants.[20] These effects and doses are comparable with those observed in animal experiments.

Administration to human volunteers of $ClO_2$, $ClO_2^-$, and $ClO_3^-$ in drinking water at increasing doses for one day did not result in any detectable alterations in blood parameters, serum or urine chemistry values, or adverse physical symptoms.[21] Similarly, no effects were detected after 84-day exposures of volunteers to 5 mg/L (0.036 mg/kg/d) of $ClO_2$, $ClO_2^-$, or $ClO_3^-$ in drinking water. For individuals identified as being deficient in glucose-6-phosphate dehydrogenase (which might make certain individuals more sensitive to the oxidative stress of disinfectants), significant changes in several blood and serum chemistry parameters were observed after an 84-day exposure to $ClO_2^-$ at 5 mg/L. There was no concurrent control group for the glucose-6-phosphate dehydrogenase-deficient individuals, however, and all measured parameters remained within the normal range.

In an epidemiological study of a community where $ClO_2$ was used as a drinking water disinfectant for 12 weeks,[22] no consistent changes were observed in any of the measured clinical parameters (hematocrit, hemoglobin, red blood cell count, white blood cell count, mean corpuscular volume, methemoglobin, blood urea nitrogen, serum creatinine, total bilirubin, reticulocyte count, and osmotic fragility). Adult exposure to $ClO_2$, $ClO_2^-$, and $ClO_3^-$ ranged from approximately 0.25 to 1.1 mg/L, 3.2 to 7.0 mg/L, and 0.87 to 1.8 mg/L, respectively. A retrospective epidemiologic study of morbidity and mortality records from a population that utilized $ClO_2$ as a primary disinfectant showed an increase in premature births, a finding that was not significant when the age of the mother was controlled.[23]

## Health effects of chlorine

Because of its oxidation potential, $Cl_2$ has been widely used as a disinfectant. In pure water, $Cl_2$ reacts to form hypochlorous acid (HOCl). As the pH of the water increases, HOCl will dissociate to the hypochlorite ion ($OCl^-$). Research on the toxicological effects of $Cl_2$, HOCl, and $OCl^-$ has been overshadowed by the investigation of various chlorination by-products such as chloramines and THMs.

Earlier studies have indicated that the ingestion of these $Cl_2$ compounds, under normal circumstances, does not directly

produce toxic effects. Two toxicological studies were conducted without any observed health effects. In the first study mice were given free available $Cl_2$ in drinking water for either 50 or 30 days (Table 2).[24] Neither autopsy nor histologic examination showed any gross abnormalities in the treated mice. In a second study, seven consecutive generations of rats were exposed to chlorinated drinking water without ill effects.[25] The incidence of malignant tumors in the exposed rats was similar to that in the control group.

Very few long-term studies on the effects of chlorinated drinking water have been performed since the Druckrey experiments.[25] However, several acute and subchronic studies have provided information that might be relevant to evaluating hazards from higher levels of $Cl_2$ exposure. The intragastric administration of chlorinated water to rats resulted in the development of "fatty" livers from the hepatic accumulation of triglycerides and fatty acids.[26] The morphological and biochemical effects were reversible within 10 days. A separate experiment demonstrated that the intragastric administration of sodium hypochlorite (NaOCl) resulted in significant reductions in the hypothalamic norepinephrine levels, which were reversible within seven days.[27]

Carcinogenic effects of $Cl_2$, HOCl, and $OCl^-$ have not been shown definitively. Sodium hypochlorite has been implicated as a cocarcinogen or tumor promoter in mice.[28] Yet, these results were disputed in a later study in which NaOCl decreased the carcinogenic response in mice.[29] Hypochlorite ion has also been associated with increased sperm-head abnormalities in male mice.[13] Further research is required to determine whether such trends would occur in larger study populations.

Several in vitro mutagenicity tests have been performed with $Cl_2$, HOCl, and $OCl^-$. Chlorine can directly produce chromosome aberrations in mammalian cells,[30] and NaOCl has been determined to be directly mutagenic in some *Salmonella* strains.[31] It is difficult to detect any mutagenic activity with $Cl_2$ in intact animals, because in seconds it would react with stomach contents, leaving no free $Cl_2$ residual. The reaction of $Cl_2$ with various precursor molecules in drinking water produces mutagenic substances,[32] and the effects from these reaction by-product chlorinated molecules would more likely present the greater risk to human exposure.

Recent research indicates that $Cl_2$ residuals as low as 2 mg/L in drinking water increased plasma cholesterol levels in pigeons that had received a diet marginal in calcium.[16] Restoration of calcium intake in the diet eliminated the hypercholesterolemia. A high lipid diet, in addition to marginal calcium intake, enhanced the hypercholesterolemic effect of $Cl_2$. Pigeons and rabbits given a calcium-deficient diet (80-percent minimum daily requirement) and exposed to NaOCl for nine or three months, respectively, showed signs of myocardial hypertrophy and atherosclerosis.[33] In two separate followup studies, however, rabbits exposed to chlorinated drinking water at levels up to 15 mg/L for as long as 90 days did not develop any noticeable changes in serum cholesterol levels, myocardial hypertrophy, or atherosclerosis.[34] The equivocal data with rabbits are being reevaluated in additional experiments.

Very little data exist on human toxicity relative to the ingestion of $Cl_2$, HOCl, and $OCl^-$, because hyperchlorinated drinking water above 25 mg/L is generally unpalatable. Ingestion of chlorinated water (5 mg/L) for 12 weeks was not associated with any adverse effects.[21]

At least 20 epidemiologic studies have been performed since 1974 to assess the relationship between water quality and different forms of cancer, because chlorination practices are known to add mutagenic and potentially carcinogenic substances to drinking water supplies. These studies have more recently focused on the effects of chlorinated by-products rather than on $Cl_2$ and its aqueous dissociation products in drinking water. Reviews have been compiled to analyze the overall findings of the epidemiologic studies.[35,36] Chlorinated drinking water has been generally associated with an elevated risk of cancer of the bladder, rectum, and colon; however, a causal relationship between chlorinated drinking water and cancer development has not been established.[37]

## Toxicology of organic disinfection by-products

From the research strategy and risk assessment viewpoint, two types of disinfection by-products should be clearly distinguished. The first type results from the reaction of organic material naturally present in source waters (humic and fulvic acids) with disinfectants. Recently, it has been recognized that residual disinfectants can also react with nutrients in the gastrointestinal tract.

Evaluating the toxicological hazards associated with the by-products of the reactions between disinfectants and background organic material is quite complex. Although specific chemicals have been clearly identified as disinfection by-products, scientists currently are unable to identify the chemicals responsible for more than 90 percent of the mutagenic activity that is generated through the reaction of $Cl_2$ with humic acids.[38] Chlorination by-products have been more thoroughly investigated than the reaction products of the alternative disinfectants such as $ClO_2$, making risk assessment even more difficult. Thus this section is limited to a review of the toxicology of specific chemicals that have been identified as by-products of disinfection (primarily chlorination).

Chlorine dioxide is a very strong oxidant that reacts with organic material to produce a variety of oxidized by-products.[39] Only limited organic by-product formation has been observed with $ClO_2$ under drinking water treatment conditions. For the most part, the toxicological significance of these $ClO_2$ by-products is unknown, because they have not been available for study. Two chemicals for which there are some toxicological data are acetaldehyde and formaldehyde, which have been found carcinogenic in animal studies. These are formed by oxidative deamination of tertiary amines and amino acids by $ClO_2$. In addition, $ClO_2$ can produce quinones and benzoquinones from a variety of substrates found in source waters, such as phenol and various chlorophenols.

Chlorination of drinking water produces many reaction by-products, most of which have not been chemically characterized. Trihalomethanes are the most familiar chlorination by-products and can occur at relatively high levels, compared with other by-products. Most of the concern about THMs results from the reported carcinogenic properties of chloroform in rats and mice.[3] Although other THMs share many of the toxicological properties of chloroform (Table 3), the results of lifetime carcinogenesis bioassays on other THMs (conducted by the National Toxicology Program) have not yet been reported.

Recently TMD-HERL sponsored a separate chloroform carcinogenicity study wherein mice and rats were exposed to chloroform in their drinking water.[40] In the previous study,[3] chloroform was administered by corn oil gavage. As reported by Jorgenson et al,[40] the results obtained with the Osborne-Mendel rat closely approximated the experimental results in the earlier National Cancer Institute bioassay. The recent study failed to confirm, however, the induction of hepatocellular carcinomas in B6C3F1 mice as reported in the earlier study. This study suggests that the carcinogenic response in the mouse liver was in some way related to the use of corn oil gavage and not entirely attributable to chloroform alone. Other toxicological properties of the THMs are described in Table 3.

The haloacetonitriles are another group of by-products formed by the chlorination of organic material in drinking water. These compounds have been shown to be mutagenic in *Salmonella*, to induce sister chromatid exchange in mammalian cells in vitro, and to induce tumors of the skin and lungs in mice.[43,44] Since the carcinogenicity of

**TABLE 2**
*Summary of oral exposure studies with chlorine and its dissociation products*

| Study | Chemical Substances | Species | Exposure Time | Toxicological Endpoint | Gavage Dose or Drinking Water Concentration—mg/L NOAEL | LOAEL |
|---|---|---|---|---|---|---|
| Blabaum and Nichols[24] | Chlorine | Mouse | 50 days | Histological changes | 100 | |
| | | Mouse | 33 days | Histological changes | 200 | |
| Druckrey[25] | Chlorine | Rat | Lifetime for 7 generations | Lifespan, fertility, growth, hematology, histology, malignancies | 100 | |
| Chang et al[26] | Sodium hypochlorite | Rat | 1 dose | Liver structural and biochemical changes | | 250 mg/kg* |
| Vogt et al[27] | Sodium hypochlorite | Rat | 1 dose | Decreased hypothalamic norepinephrine levels | | 250 mg/kg* |
| Meier et al[13] | Sodium hypochlorite | Mouse | 5 days | Sperm-head abnormalities | | 4 mg/kg/d |
| | Hypochlorous acid | Mouse | 5 days | Sperm-head abnormalities | 8 mg/kg/d | |
| Revis et al[16] | Chlorine (pH 8.5) | Pigeon | 90 days | Decreased plasma thyroid hormones, increased plasma cholesterol, increased plaque size | | 2 |
| Lubbers et al[23] | Chlorine | Human | 1 day | Hematologic, serum chemistry, urinalysis | 24 | |
| | | Human | 84 days | Hematologic, serum chemistry, urinalysis | 5 | |

*Assuming rat weight = 200 g

these compounds remains to be confirmed by lifetime animal studies, they are considered genotoxic for purposes of this article. General toxicological properties and developmental effects of the haloacetonitriles have recently been reported.[45,46]

Several other classes of chlorination by-products have been reported—haloacids, chlorophenols, and chlorinated ketones. The diverse toxicological properties of these compounds also are shown and referenced in Table 3.

## Current toxicology research areas

Atherosclerosis, with its accompanying complications, is one of the most serious health problems affecting American adults. Animal studies, in which the food is marginal in calcium, suggest that various disinfectants may elevate serum cholesterol values and produce signs of cardiac hypertrophy and arteriosclerosis.[16,33] Current information is too limited to confirm or to refute this effect in humans, but evidence suggests that the human population may have an increased cardiovascular disease risk from chronic exposure to disinfected drinking water.[55] Calcium intake for certain segments of the US population is less than that administered in the animal experiments. For example, the median calcium intake by blacks falls below the recommended daily requirement by age 18, whereas the median calcium intake of whites falls below that level by age 35.[56] An association has been established between drinking water of low hardness (low calcium) and cardiovascular disease mortality in humans.[57] Although Bull and McCabe[58] presented evidence that surface water supplies treated only by chlorination present a greater risk for contributing to arteriosclerotic heart disease than both groundwater and surface water supplies treated by chlorination and other processes, they also describe the complex issues involved in assessing the extent to which any additional cardiovascular disease risks are attributable to chlorination.

To better understand whether there is a relationship between disinfection practices and cardiovascular disease, TMD-HERL is conducting the following studies: additional independent experiments to verify the cardiovascular effects seen in pigeons, studies involving primates exposed to disinfectants, a clinical study to investigate the effects of disinfectants on human lipid metabolism,[59] and an epidemiologic study to investigate the roles of calcium intake in human cardiovascular disease and to measure potential differences in blood pressure, serum lipids, and cardiovascular disease risk in populations supplied with chlorinated and nonchlorinated drinking water.[55]

Another area that must be critically evaluated is the generation of by-products that form in the gastrointestinal tract upon ingestion of drinking water containing a residual disinfectant. Initial experiments indicate that by-products similar to those identified in drinking water are formed in vivo following high doses of disinfectant. In fact, NaOCl ingestion has been shown to produce carcinogenic by-products such as chloroform, other THMs, and haloacetonitriles in the gastrointestinal tract.[60,61] Sperm-head abnormalities in mice from NaOCl also indicates the potential in vivo formation of mutagenic and potentially carcinogenic by-products.[13] Research is being conducted to identify and characterize chlorination by-products formed in vivo.

In evaluating the health impacts of $ClO_2$, the potential of in vivo formation of iodinated organics from iodine present in body fluids (saliva and gastric juices) should be of concern. The antithyroid effect of $ClO_2$ appears most likely to be an indirect effect. Chlorine dioxide oxidizes iodine to its reactive elemental state, causing reactive iodine to bind to organic substances or nutrients present in the gastrointestinal tract.[62,63] The present hypothesis is that some of these iodinated compounds may be thyroid antagonists or thyromimetic agents that act by enzymatic or feedback inhibition on thyroxine synthesis.[64] The questions of in vivo formation of iodinated organics, their chemical and toxicological properties, as well as the alteration of iodide transport and bioavailability are under investigation.

## Summary and conclusions

The research program at TMD-HERL has revealed that the drinking water disinfectants and disinfection by-product issue is more complex than previously thought. Initially, the primary concern was the production of THMs from chlorination of drinking water. At least one of these reaction by-products, chloroform, had been identified as a carcinogen. The solution to this problem was to use alternative disinfectants such as $ClO_2$ that did not produce THMs. The following additional problems have been identified with the disinfection practices of $Cl_2$ and $ClO_2$.

- A great variety of chlorination by-products has been identified in addition to THMs, none of which have been well characterized toxicologically. Many of the identified by-products have been demonstrated to possess mutagenic or carcinogenic properties as well as other toxicological properties. Care should be taken not to prematurely indict the use of $Cl_2$, since less is known about the reaction by-products of the alternative disinfectants.
- Many of the by-products formed in water are also formed in the gastrointestinal tract of experimental animals when directly exposed to $Cl_2$ solutions. This raises a concern about using high residual levels of disinfectant.
- Chlorine dioxide appears to alter the metabolism and bioavailability of iodine, which causes the formation of iodinated organics in vivo. The toxico-

**TABLE 3**

*Summary of health effects associated with chlorination by-products*

| Chemical Class | By-product | Toxicological Effects | References |
|---|---|---|---|
| Trihalomethanes | Chloroform | Carcinogenic, hepatotoxic, renal toxic | 3, 40, 41, 42 |
| | Dichlorobromomethane | Hepatotoxic, renal toxic | 41, 42 |
| | Dibromochloromethane | Hepatotoxic, renal toxic | 41, 42 |
| | Bromoform | Hepatotoxic, renal toxic | 41, 42 |
| Haloacetonitriles | Chloroacetonitrile | Genotoxic, developmental | 43, 44, 45 |
| | Dichloroacetonitrile | Mutagenic, genotoxic, developmental | 43, 44, 45 |
| | Trichloroacetonitrile | Genotoxic, developmental | 43, 44, 45 |
| | Bromochloroacetonitrile | Mutagenic, genotoxic, developmental | 43, 44, 45 |
| | Dibromoacetonitrile | Genotoxic, developmental | 43, 44, 45 |
| Haloacid derivatives | Dichloroacetic acid | Metabolic derangements, neurotoxic, ocular lesions, aspermatogenesis | 47, 48, 49, 50 |
| | Trichloroacetic acid | Increased hepatic peroxisomes | 51 |
| Chlorophenols | 2-Chlorophenol | Fetotoxic, tumor promoter | 52, 53 |
| | 2,4-Dichlorophenol | Fetotoxic, tumor promoter | 52, 53 |
| | 2,4,6-Trichlorophenol | Carcinogenic | 54 |
| Chlorinated ketones | 1,1-Dichloropropanone | Mutagenic | 38 |
| | 1,1,1-Trichloropropanone | Mutagenic | 38 |
| | 1,1,3,3-Tetrachloropropanone | Mutagenic | 38 |

logical significance of this event is currently under investigation and may explain the antithyroid effect seen with $ClO_2$. This interference of normal thyroid function seems to have lasting behavioral effects when young animals are involved.

- At levels as low as 50 mg/L, $ClO_2^-$ produces signs of hemolytic stress in animals. Although probably not critical for normal humans, some concern must be expressed for those individuals who are sensitive to hemolytic agents (i.e., deficient in glucose-6-phosphate dehydrogenase) or who are taking medication that can produce hemolytic anemia. Because of the concerns about the hematopoietic and thyroid effects of $ClO_2$ and $ClO_2^-$, it has been recommended that the total residues of these products not exceed 1 mg/L in finished drinking water.[65]
- Chlorine at low doses (2 mg/L), coupled with a diet marginal in calcium, elevated serum cholesterol and produced evidence of atherosclerosis in pigeons receiving normal and high lipid diets. At higher doses (15 mg/L), $ClO_2$ has been shown to elevate serum cholesterol only when the animals were maintained on a marginal calcium, high lipid diet. This effect has been reproduced in pigeons but not in rabbits. If these experiments are borne out by further studies, this finding could be of significant consequence, because a high fat diet and low calcium consumption are common in the United States.

A safe public water supply is not possible without disinfection in the United States. Risks from microbiological hazards must clearly be included in the overall evaluation of hazards arising from water treatment and from protecting the water against deterioration during distribution. A coordinated program for defining health hazards associated with alternative forms of disinfection must be continued so that the safest alternative can be determined. Currently there is no clear indication of one disinfectant being superior to another when considering toxicological risks. Additional research must be conducted to provide the necessary data for risk assessment of the alternative disinfectants.


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